# Bandolier 84

What do we think?
What do we know?
What can we prove?

**Evidence-based health care** **£3.00** **February 2001 Volume 8 Issue 2**


Choosing articles for ***Bandolier*** is often quite straightforward. Good quality evidence that is either understandable or can be explained, and about topics that are common, just about sums it up. If that evidence is not there, occasionally a quick review is very helpful.

The MMR and autism argument has been outside the straightforward, but several recent publications shed much more light. So this month we have examined evidence linking them, and ***Bandolier*** agrees with almost every other healthcare professional and government health service that there is no link.

The problem is that arguments, especially in the media, get mixed. They start by asking about the vaccination link, and end up by engaging in discourses about the cause of autism, how fast it is growing, and who or what is to blame. There are no easy answers.

There is evidence that better services increase apparent autism rates because of case finding [1]. There appears to be evidence linking autism to viral pandemics [2]. Some gene-environment interaction may be a factor [3]. There are systematic reviews [4, 5] on screening and diagnosis. But there's no answer and no certainty that we could find. The lesson is that with a little time and a helpful librarian it is possible to know a lot quite quickly, even is that is not enough.


1 RE Hillman et al. Prevalence of autism in Missouri: changing trends and the effect of a comprehensive state autism project. Missouri Medicine 2000 97: 159-63.
2 A Ticher et al. Circannual pattern of autistic births: reanalysis in three ethnic groups. Human Biology 1996 68: 585-92.
3 EA London. The environment as an etiologic factor in autism: a new direction for research. Environmental Health Perspectives 2000 108 Suppl 3: 401-4.
4 MM Bristol-Powers, G Spinella. Research on screening and diagnosis in autism: a work in progress. Journal of Autism and Developmental Disorder 1999 29: 435-8.
5 PE Tanguay. Journal of American Academy of Child and Adolescent Psychiatry 2000 39:1079-95.


## In this issue





## MMR VACCINATION

More media circuses about vaccinating children with MMR, and the "association" of MMR vaccination with autism and inflammatory bowel disease. Frightening stuff, but much heat and little light. One of ***Bandolier***'s informal team asked us to look out the evidence. There's much, mostly from exemplary public health work in Finland, and it shows conclusively that vaccination with MMR does not cause autism or bowel problems.

### Background

In Finland, much of the push for immunisation came from the large number of recruits or conscript soldiers who fell ill. In the days before immunisation more than a quarter of them had clinical mumps, and a third of them had orchitis, a quarter of those had bilateral orchitis and a quarter of them were rendered sterile. Mumps contracted during military service was a major cause of infertility, and a major cause of hearing impairment in children, as well as later deafness.

Rubella was also common, with about 1 case per 1000 people a year. Again there was an association with hearing impairment in children, and congenital rubella syndrome was a problem. As a reminder to those of us who forget that infectious diseases are merely inconvenient, when rubella infection occurs during pregnancy, especially during the first trimester, foetal infection is likely and often causes congenital rubella syndrome (CRS), resulting in abortions, miscarriages, stillbirths, and severe birth defects. Up to 20% of the infants born to mothers infected during the first half of pregnancy have CRS. The most common congenital defects are cataracts, heart disease, sensorineural deafness, and mental retardation.

### Programme and follow up

In 1982 a major effort was put into vaccinations using a triple MMR vaccine (almost always that produced by Merck & Co, which is known by different names in different parts of the world). The programme involves 1000 child health centres, catch up programmes, and military recruits. Two million people (40% of the population) have received 3.5 million doses, and coverage is over 95%.

A national reporting system for mumps, measles and rubella is in force, policed by the National Public Health Institute. Serological confirmation of reported cases has been a requirement since 1987.

In the event of a possible serious adverse event (defined as any temporal association without limit of time between MMR and a life-threatening disorder, triggering of a chronic disease or hospital admission), a form was then completed and forwarded to a central office with a serum sample. A second form and second sample followed two weeks later. Forms, envelopes and collection tubes were available at child health centres and hospitals.

## Results

The total number of reported vaccine-associated events in 1.8 million people having 3 million vaccinations was 437. Of these, potentially serious adverse events occurred in 169 people, 79 of whom went to hospital. These 169 people were subject to detailed scrutiny.

The details of the potentially serious adverse events are shown in the Table. About half the reported adverse events could be ascribed to other factors (like other vaccinations given with MMR) on clinical, serological and epidemiological analyses. No event had an incidence of more than 1 case per 100,000 doses of vaccine.

There were no cases of autism, and no cases of ulcerative colitis, Crohn's disease or any chronic disorder affecting the gastrointestinal tract.

## Other evidence

Other evidence rejecting a causal link between MMR vaccine and autism comes from a retrospective study of about 500 cases of autism in North Thames [4]. Records of children with autistic disorders born since 1979 were identified, and their clinical details examined. Immunisation data was obtained from a separate computerised register.

The results showed that the incidence of autism (core autism, atypical autism and Asperger's syndrome) rose from low levels in 1979 to much higher levels by the early 1990s. This was a continuous trend, with no evidence of a step-up after the introduction of MMR in 1987. There were no differences in age at diagnosis between those vaccinated with MMR and those not vaccinated. No other analysis showed any association between autism and MMR vaccination. There was no temporal clustering between MMR vaccination and diagnosis of autism.

## Comment

Whenever we take a child to be vaccinated, we are aware that there is a balance between benefit and harm, just like any medical intervention. The potential for harm from infectious disease like measles, mumps and rubella is significant, but too often forgotten because outbreaks of these infectious disease are thankfully rare. Unvaccinated children contracting these diseases have a potential for serious and long-lasting harm. The history of mumps and rubella in Finland [2] makes chilling reading as the litany of harm from these infectious diseases unfolded.

The effects of measles can be seen from a recent outbreak in Ireland. The Irish National Disease Surveillance Centre reports more than 1220 cases of measles in 2000; two children in north Dublin died. There is also a report of an outbreak in the Netherlands. More than 2300 cases arose in a community philosophically opposed to vaccination. Three children died, 53 were hospitalised, and four developed encephalitis. That's one death for every 700 children infected with measles in countries with some of the best healthcare in the world. And the Oxford Textbook of Medicine informs us that measles deaths have dropped from two million a year in 1987 to only 900,000 now because of immunisation.

**Table 1: MMR-associated adverse events found during vaccinating 1.8 million Finns with 3 million doses of MMR vaccine**

| Event | Total number of events | Number with possible MMR association | Incidence per 100,000 doses of vaccine |
|---|---|---|---|
| **Death** | 1 | 0 | 0.00 |
| **Allergic disorders** | | | |
| Anaphylaxis | 30 | 14 | 0.50 |
| Urticaria | 30 | 25 | 0.80 |
| Asthma | 10 | 5 | 0.20 |
| Henoch-Schönlein purpura | 2 | 1 | 0.03 |
| Stevens-Johnson syndrome | 1 | 1 | 0.03 |
| **Neurologic disorders** | | | |
| Febrile seizure | 52 | 28 | 0.90 |
| Epilepsy | 3 | 1 | 0.03 |
| Undefined seizure | 4 | 2 | 0.07 |
| Encephalitis | 4 | 3 | 0.10 |
| Meningitis | 4 | 0 | 0.00 |
| Guillain-Barré syndrome | 2 | 2 | 0.07 |
| Transient gait disturbance | 5 | 5 | 0.30 |
| Confusion during fever | 3 | 2 | 0.07 |
| **Miscellaneous** | | | |
| Pneumonia | 12 | 5 | 0.20 |
| Orchitis | 7 | 1 | 0.03 |
| Diabetes | 3 | 0 | 0.00 |

By contrast, harm is much, much less common. In the Finnish study [3] there were no more than three adverse effects for every 100,000 doses of vaccines. While even these adverse effects were best avoided, the balance between benefit and harm is very much on the side of benefit. There were no cases of autism in 1.8 million people immunised. There were no cases of inflammatory bowel disease. The rule of three (***Bandolier*** 23) tells us that we can be 95% confident that autism or inflammatory bowel disease occur no more frequently than in 1 in 600,000 cases of MMR vaccination.

And this is good, solid evidence. The study was prospective. The study was comprehensive. The study had a long (14 year) follow up. The study had no artificial cut point for parent or professional to link any childhood problem with MMR vaccination. And it was big, and supported by other epidemiological studies [4].

The evidence purported to link MMR to autism and inflammatory bowel disease [5] concerned 12 children referred because of loss of skills plus gastrointestinal problems. This was associated with MMR by the parents in eight cases. The authors themselves say that they did not prove a link, which would be difficult, since anyway eight or nine out of every 10 children is vaccinated with MMR.

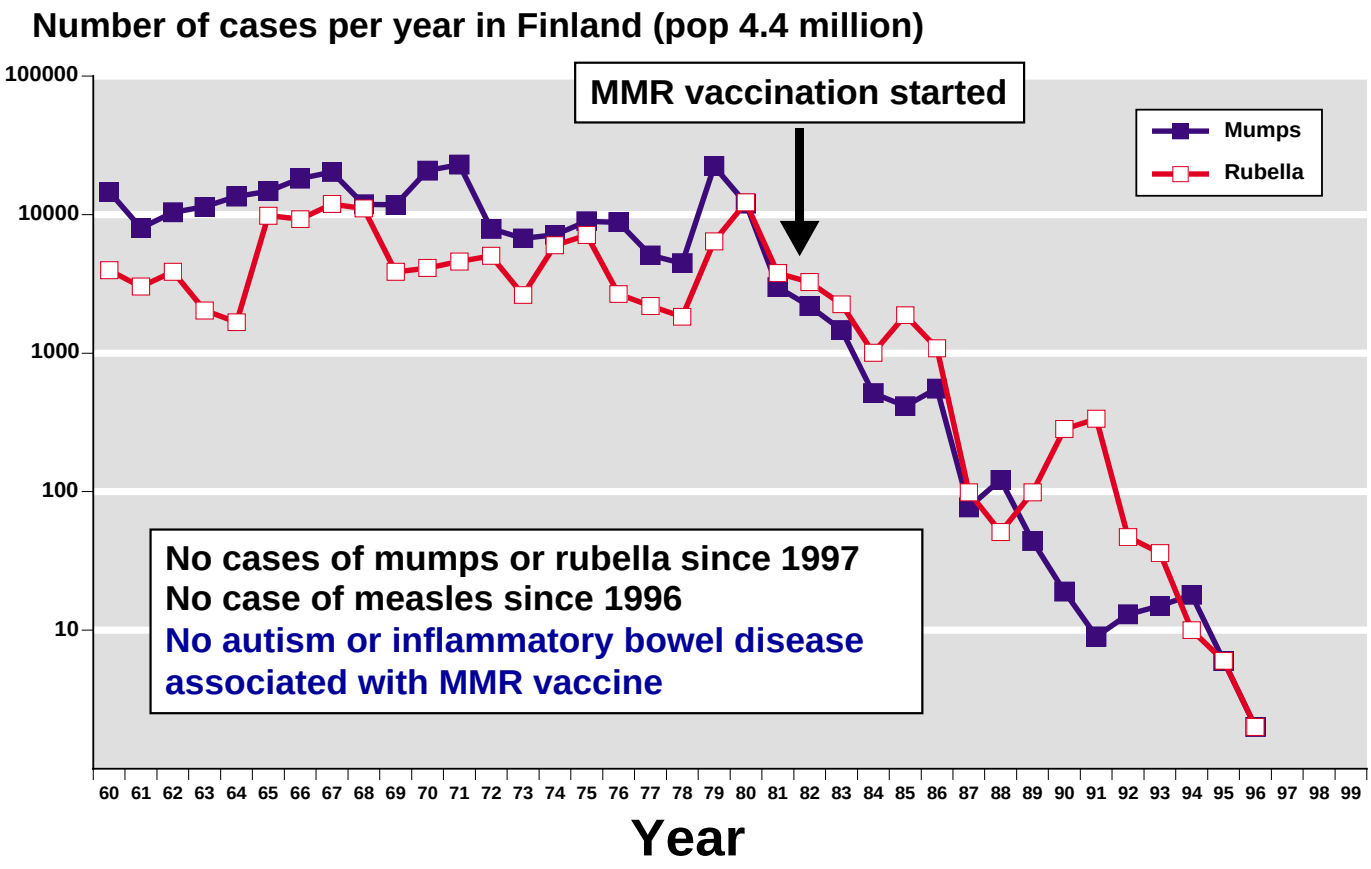
Finland is a small enough county that it is possible to be in touch with heroes (sharing Sibelius's drinking haunts, or sniffing the tobacco in Mannerheim's study). Perhaps the lesson is that we should take people's obvious concerns about adverse effects of healthcare seriously. People would respect healthcare more if larger prospective studies were done to collect rare but serious harm information. Bear in mind also that there is more than one MMR vaccine. The Finnish study relates to only one of them. One vaccine was withdrawn in the early 1990s [6], and the UK epidemiological study [5] does not give the make of vaccines used.

But the bottom line is this. The evidence and the textbooks tell us that measles in non-immunised populations like religious minorities can be as high as 1 in 300 or so. The chance of harm from immunisation is very much less, and much less severe.

References:


1 H Peltola et al. No measles in Finland. Lancet 1997 350: 1364-5.
2 H Peltola et al. Mumps and rubella eliminated from Finland. JAMA 2000 284: 2643-2647.
3 A Patja et al. Serious adverse events after measles-mumps-rubella vaccination during a fourteen-year prospective follow up. Pediatric Infectious Diseases Journal 2000 19: 1127-1134.
4 B Taylor et al. Autism and measles, mumps, and rubella vaccine: no epidemiological evidence for a causal association. Lancet 1999 353: 2026-2029.
5 AJ Wakefield et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. Lancet 351: 637-641.
6 MR Kiln. Autism, inflammatory bowel disease, and MMR vaccine. Lancet 1998 351:1358.


**Figure 1: Number of cases of mumps and rubella in Finland before and after the inception of widespread MMR vaccination programme in 1982**



# ANTIDEPRESSANT DRUG ADHERENCE

One of those battles that seems to rage in the background is the question of whether SSRIs produce better patient compliance than other antidepressants. A major problem is how to measure compliance, and one measure which has been used is the number of people who withdraw from clinical trials. A new Cochrane review does more than most reviews (of which a number are to be found in the literature) to help us think about this.

It is important, because this question is at the heart of which treatment should come first in the treatment of depression. If efficacy and harm are balanced, cost rules. If efficacy and harm are not balanced, then the question of cost-effectiveness emerges, and cost-effectiveness in healthcare systems is not an exact science.

## Review

The review sought randomised trials comparing SSRIs with other antidepressants in patients suffering from depression diagnosed by any criteria. The outcomes extracted were the number of people withdrawing during the study in total, and those withdrawing due to inefficacy and those withdrawing due to adverse events. Several electronic databases were searched, including a specialist depression register, with hand searching of specialist journals plus attempts to obtain unpublished material. There was no language restriction. Studies were grouped by older tricyclics (amitriptyline, imipramine), newer tricyclics (clomipramine, desiprameine, for example) and heterocyclics (maprotiline, mianserin, for example).

## Results

There were 136 trials that met the inclusion criteria. Their duration was four weeks to one year, but most were longer than six weeks, and over half were conducted in an outpatient setting. Most of the studies enrolled patients suffering from major depression, using standard diagnostic criteria.

There were fewer total withdrawals with SSRIs. On average total withdrawals were 27% with SSRIs and 30% for comparator drugs. More SSRI withdrawals due to lack of efficacy were counterbalanced by fewer withdrawals due to adverse events.

There was considerable variability in adverse event withdrawal rates in individual studies, best exemplified by the large data sets for amitriptyline (Figure 1) and imipramine (Figure 2). Group sizes in these comparisons varied between 10 and 380 patients. Of the 122 separate groups, 80 had 50 or fewer patients, 37 between 51 and 100, 12 between 101 and 200 and three over 200 patients.

Adverse event withdrawals for particular drug comparisons with SSRIs are shown in Table 1 and Figure 3 for those where there were at least three trials. SSRIs had significantly fewer adverse event withdrawals than amitriptyline, imipramine and clomipramine, with numbers needed to treat to prevent one adverse event withdrawal of about 15 to 20. Other comparisons either had no significant difference or there were fewer than 200 patients in the comparator group. Figure 3 shows the 95% confidence interval for the absolute adverse event withdrawal rate. Where the numbers of patients was small, the confidence interval was wide.

**Figure 1: Adverse event withdrawals in trials comparing SSRI with amitriptyline**

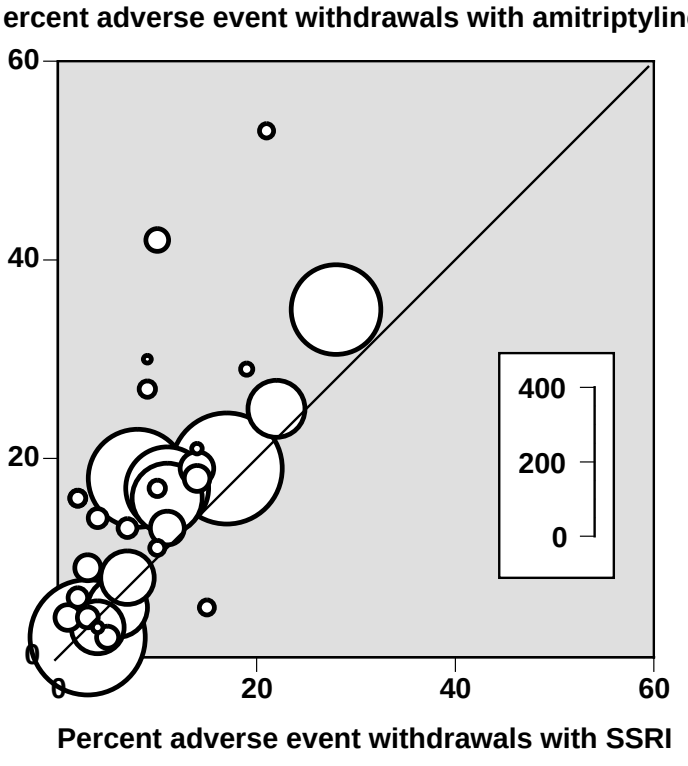



**Figure 2: Adverse event withdrawals in trials comparing SSRI with imipramine**

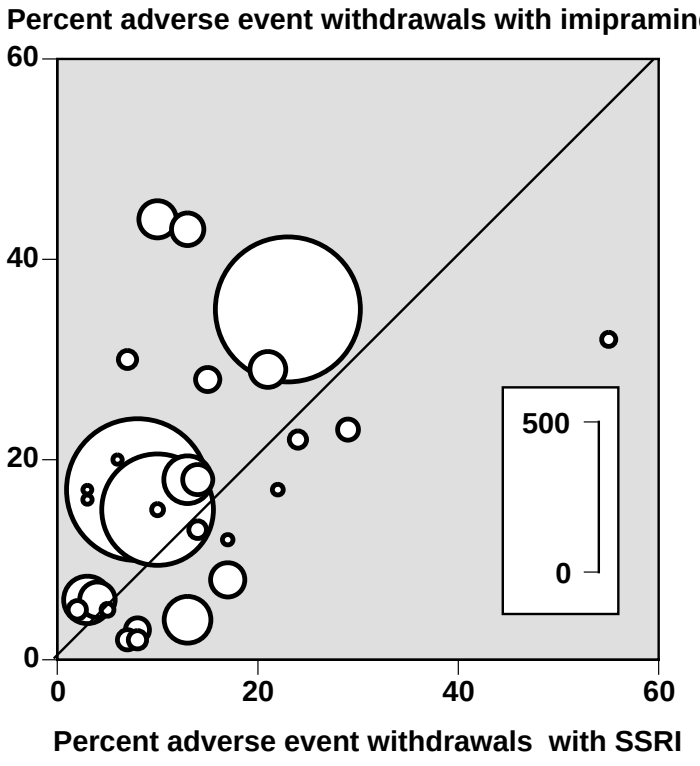


**Table: Adverse event withdrawals in comparisons of particular antidepressants and SSRIs**

| Comparison SSRI and - | Number of trials | Antidepressant Number/ total | Antidepressant Percent (95%CI) | SSRI Number/ total | SSRI Percent (95%CI) | Relative benefit (95%CI) | NNT (95% CI) |
|---|---|---|---|---|---|---|---|
| Amitriptyline | 32 | 231/1563 | 15 (13-17) | 184/1670 | 11(10-13) | 1.4 (1.1 to 1.8) | 27 (16 to 69) |
| Imipramine | 29 | 301/1508 | 20 (18-22) | 233/1844 | 13 (11-14) | 1.8 (1.4 to 2.4) | 14 (10 to 22) |
| Clomipramine | 11 | 117/1105 | 11 (9-12) | 74/1021 | 7 (6-9) | 1.6 (1.2 to 2.1) | 23 (14 to 55) |
| Maprotiline | 7 | 40/451 | 9 (6-12) | 27/452 | 6 (4-8) | 1.5 (0.9 to 2.3) | not calculated |
| Dothiepin | 5 | 11/171 | 6 (3-10) | 29/173 | 17 (11-22) | 0.4 (0.2 to 0.8) | -10 (-6 to -28) |
| Mianserin | 4 | 15/113 | 13 (7-20) | 20/110 | 18 (11-25) | 0.7 (0.4 to 1.3) | not calculated |
| Doxepin | 3 | 29/197 | 15 (10-20) | 38/200 | 19 (14-24) | 0.8 (0.5 to 1.2) | not calculated |
| Desipramine | 3 | 10/70 | 15 (6-22) | 2/71 | 3 (0-7) | 3.7 (1.1 to 12) | 9 (5 to 58) |

## Comment

Firstly, this was a fine and thorough review, short and readable, and with a useful discussion about the likely importance of dose. SSRIs were grouped together, so no comments can be made about withdrawals for particular SSRIs.

Secondly, it shows the importance of size in determining small differences between groups. With the information we have, we can be sure that adverse event withdrawal rates are lower with SSRIs than amitriptyline and imipramine. For others there is doubt. For clomipramine, for instance, there are significantly more adverse event withdrawals than for SSRIs (Table 1), but the percentage of withdrawals is no different than the overall rate for SSRIs (Figure 3).

Why the uncertainty? This comes from three main areas – dose, collecting adverse event data, and size.

- Higher doses of medicines are likely to elicit greater adverse event rates. The results that we are presented with make no allowance for dose, so this could be a contributory factor.
- Collecting adverse event information using diaries elicits higher rates of adverse events than spontaneous reporting [2]. Different collection methods may also influence withdrawal rates, and definitions of withdrawals may not always be the same.

**Figure 4: SSRI adverse event withdrawal rate and size of trial. Vertical line is overall mean**

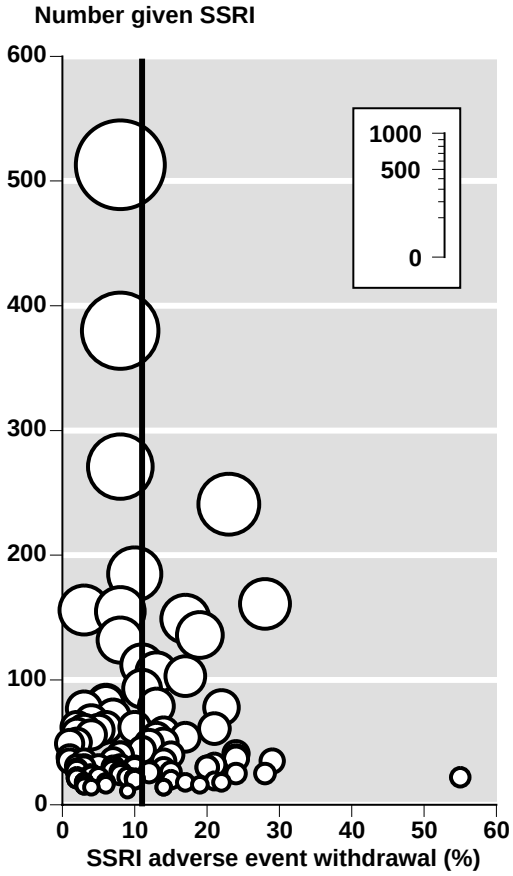
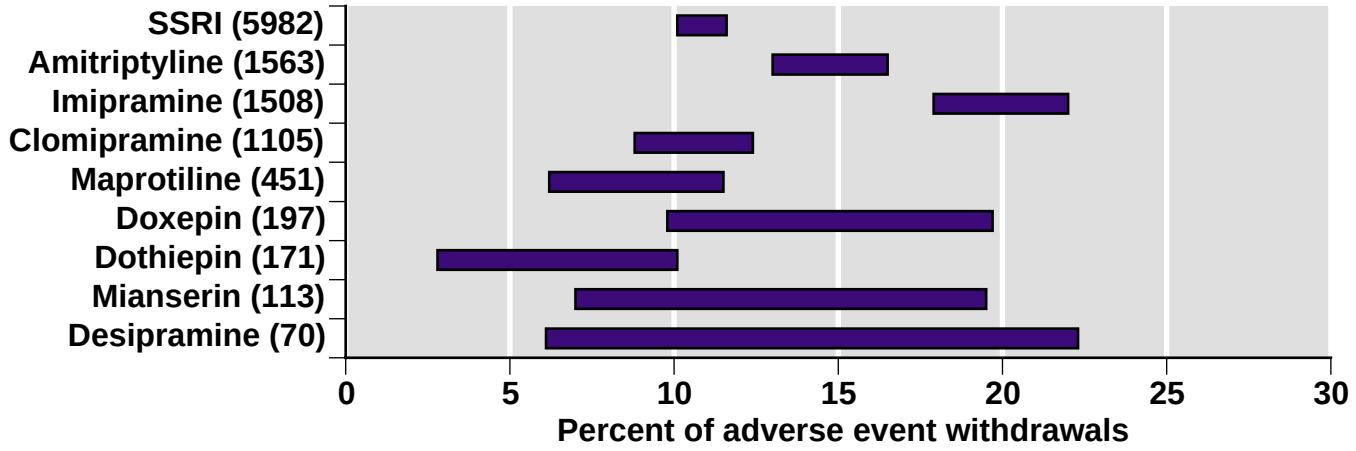



**Figure 3: Absolute adverse event withdrawal rates (95% CI). Total in parenthesis**



- Size is crucial, because smaller amounts of information are more susceptible to the random play of chance. Figure 4 shows the SSRI adverse event withdrawal rates in 100 trials according to the size of the SSRI group. Below 200 patients the rates are highly variable. For many comparisons (Table 1) we have fewer than 200 patients, reflecting the variable SSRI withdrawal rates and affecting the chances of showing any true difference, let alone the size of that difference.

So our conclusion is that while there are lower adverse event withdrawal rates with SSRIs, extrapolating from those to real-life situations or whole healthcare systems will not be easy.

References:
1 C Barbui et al. Selective serotonin reuptake inhibitors versus tricyclic and heterocyclic antidepressants: comparison of drug adherence. In: The Cochrane Library, Issue 4, 2000. Oxford: Update Software.
2 JE Edwards et al. Reporting of adverse effects in clinical trials should be improved. Lessons from acute postoperative pain. Journal of Pain and Symptom Management 1999; 18:427-37.

# HYPERTENSION AND WEIGHT LOSS

***Bandolier*** is interested in how lifestyle can keep people out of the hands of the healthcare system. It is better for individuals and better for healthcare systems. Being overweight is a bad thing for many reasons, one of which is that obesity is associated with high blood pressure. ***Bandolier*** 51 reported that weight loss and salt restriction could result in patients on antihypertensive medicines not needing to use them. Another large RCT now reinforces this message, emphasising that losing weight reduces blood pressure and helps stop people becoming patients [1].

## Study

There were just under 1200 participants. They were overweight, with a body mass index of 25 to 37 (mean 31), and with a mean weight of 99 kg for men and 84 kg for women. They took exercise only once or twice a week, and their mean systolic blood pressure was 127 mmHg and diastolic 86 mmHg. None was being treated for hypertension at the start of the trial, or for diabetes, renal disease, or cardiovascular disease. Their mean age was 43 years.

Randomisation was to weight loss or usual care. Weight loss had a target of 4.5 kg during the first six months, maintained over a further 30 months. Individual counselling sessions were followed by 14 group meetings, and thereafter six bi-weekly sessions, and then monthly sessions. Other options were available after 18 months. Behavioural self-management was the intention, with monitoring with food and activity diaries. Dietary interventions focused on reducing fat, sugar and alcohol consumption. The target was a caloric intake that allowed individuals to lose weight, but loss of more than 0.9 kg a week was discouraged. Weight and blood pressure were recorded every six months, by staff blinded to treatment assignment. Follow up was over 90%.

## Results

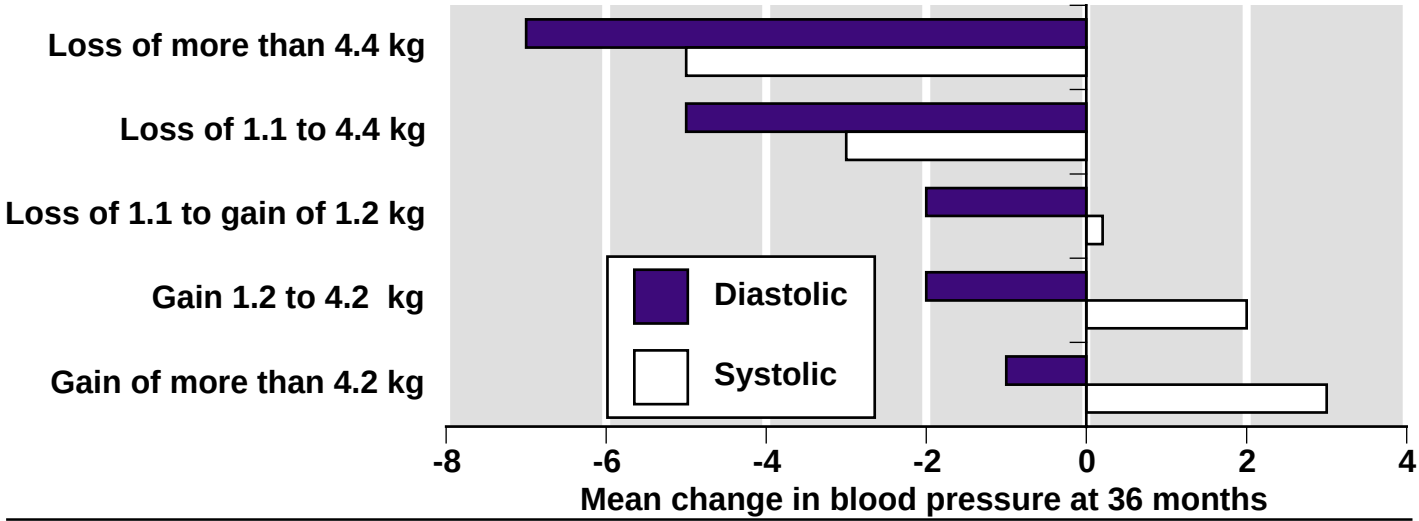
The control group of 596 patients gradually increased their mean weight by just under 2 kg over 36 months. The intervention group lost an average of 4.4 kg over the first six months, but weight gradually increased so that by 36 months the mean was just 0.2 kg below the starting weight, but 2 kg below the control group.

The intervention group had a mean reduction in systolic blood pressure of 2.7 mmHg below control at six months, and 0.9 mmHg at 36 months.

Blood pressure was highly related to the extent and duration of weight loss. For instance, blood pressure at 36 months was very much lower in those who achieved and maintained a weight loss of at least 4.4 kg, whereas it was minimally reduced or even increased in those with no weight loss or who actually gained weight (Figure).

- In those whose weight loss at six and 36 months was 2.5 kg or less, there was no change in blood pressure.
- In those who initially lost 4.5 kg or more at six months, but whose weight loss at 36 months was less than 2.5

**Figure: Mean change in blood pressure by quintiles of weight loss at 36 months**



kg, initial blood pressure reductions had not been maintained.

- In those who had lost at least 4.5 kg by six months and maintained that loss, an initial average fall in systolic and diastolic blood pressure of 8 or 9 mmHg was maintained.

Weight loss also prevented the onset of hypertension defined as a systolic blood pressure of at least 140 mmHg, a diastolic blood pressure of 90 mmHg, or prescription of antihypertensive medicines. The risk ratios (all we are given) were significantly below 1 for the intervention compared to the control group. For successfully maintained weight loss compared to controls, the risk ratio was 0.35 (95% CI 0.2 to 0.6).

## Comment

There was a direct dose-response relationship. Lose more weight and keep it off, and your blood pressure will fall more and the fall will be maintained longer. This is important information for a relatively young (43 years) but overweight and unfit group of people without established hypertension. The lesson is that without action they will gain more weight, their blood pressure will rise, and they will need antihypertensive medicines.

That's not always a good thing, because effective though they may be, efficacy comes with a price. Without feeling much different one goes from being a person to being a patient. The medicines have adverse effects, and those are problematical for many people.

Weight loss plus exercise is a good way of preventing this. Another good example of the benefits of healthy living. The question is one of delivery. Perhaps we need to have a little health economic modelling to demonstrate the personal and societal benefits of putting more effort into delivering a health service rather than a sick service.

References:
1 VJ Stevens et al. Long-term weight loss and changes in blood pressure: results of the trials of hypertension prevention, phase II. Annals of Internal medicine 2001 134: 1-11.

# IMPROVED DIABETIC CONTROL REDUCES HEALTHCARE COSTS

A major goal of diabetes care is better control of blood glucose. Reducing levels towards normal more of the time reduces tissue damage, organ damage, and all the horrid consequences of poorly controlled disease. That is a good enough reason for better glycaemic control, but another is that better control, by reducing the need for more intense medical care later, should reduce healthcare costs. That conclusion usually comes from economic modelling, but a new study from Seattle [1] shows in that real patients in a real setting better control equals reduced cost.

## Study

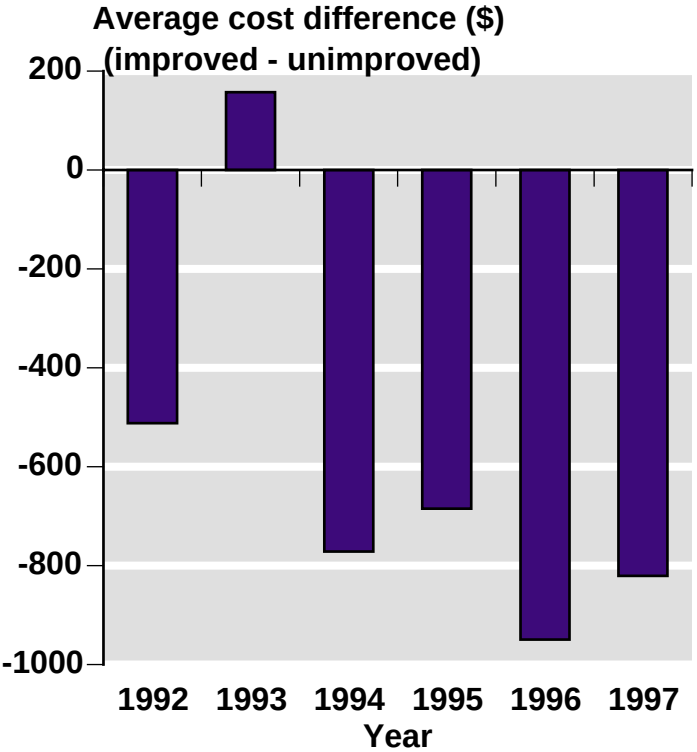
The study was conducted in a health maintenance organisation of about half a million people around Puget Sound. Diabetics in the scheme from 1992 and with at least annual measurements of glycated haemoglobin (HbA1c) formed the study population. These 4744 patients were divided into those 732 with HbA1c levels that decreased by at least 1% between 1992 and 1993, and where the decrease was maintained to 1994. The other 4012 unimproved patients formed the control group. Demographic information and healthcare utilisation and costs were collected from administrative databases (and this particular HMO has a strong research background). Cost data was expressed in 1997 US$.

## Results

The average age was 60 years with a heavy preponderance of type 2 diabetes. Patients saw a primary care physician 7-8 times a year on average, with four specality care visits a year. The improved cohort had higher baseline rates of foot ulcer, eye disease, heart attacks and strokes, but not ischaemic heart disease. Baseline HbA1c for improved patients was 10% and for those who did not improve it was 8%.

Total healthcare costs over the period 1992 to 1997 were lower by $685 to $950 a year for those patients whose HbA1c improved (Figure) than in those whose HbA1c did not improve, after an initial rise in 1993. This mirrored a reduction in hospital admissions, and fewer specialty care and primary care visits. Cost savings were most impressive in those whose initial HbA1c was above 10%, but savings occurred at all levels of HbA1c. Cost savings occurred in diabetics with cardiovascular disease, diabetics with other complications, and diabetics with no complications.

**Figure: Average annual cost differences between improved and unimproved diabetics (US$ 1997)**



## Comment

This is a thorough examination of the cost-saving effects of better glycaemic control, mainly in type 2 diabetics. It demonstrates in a real population what has been previously theorised, that better glycaemic control will result in lower healthcare costs, and that this occurs within two years and is sustained.

There are two lessons. First is the obvious one that here is a lesson about investment in services. Invest now for better health at eventually lower costs. The second is about data sources. HMOs in the USA, if they have done one thing only, have provided excellent ways of collecting real-life cost and benefit information. It is curious that national services in Europe, and especially the UK, couldn't hope to provide anything like this quality of data.

References:
1 EH Wagner et al. Effect of improved glycemic control on health care costs and utilization. JAMA 2001 285: 182-189.

# FITNESS AND ATHEROSCLEROSIS PROGRESSION

Good cardiorespiratory fitness, usually a product of exercise, is associated with lower risks of bad things happening, like heart attacks, strokes, and other vascular events. One question unanswered till now has been the extent to which exercise and fitness slows the progression of atherosclerosis. A study from Finland [1] shows that it does in middle-aged men, a finding that again raises some questions about how much effort should be put into health promotion.

## Study

This was a complicated study in some ways, and difficult to précis because of the very large number of measurements made. There were 854 men chosen randomly from the population of Kuopio in eastern Finland, and who were 42, 48, 54 or 60 years old between 1984 and 1989. Fitness was assessed using a maximum exercise test and measuring oxygen consumption (expressed as mL/kg/minute during maximum exercise). At about the same time carotid atherosclerosis was measured using ultrasound at the 1.5 cm distal end of the right and left common carotid artery. Four measures of atherosclerosis were used, and repeated four years later.

## Results

Men with lower cardiorespiratory fitness at baseline had much higher levels of coronary heart disease, heart failure, stroke history, claudication asthma and diabetes than those who had high cardiorespiratory fitness.

Over four years men with higher fitness levels had significantly lower indices of atherosclerosis development than those with lower levels of fitness. After adjusting for factors like age, smoking and so on, the energy expenditure of conditioning physical activity and its frequency were associated with slower increase in carotid atherosclerosis. Conditioning physical activity was walking, jogging, cross county skiing, cycling, swimming, rowing, ball games, dancing or weightlifting.

## Comment

One of the most interesting parts of this report was the discussion, because increasing maximum oxygen consumption is only partly a reflection of exercise undertaken. Other factors, including genetics, diet and weight all contribute. But there is little doubt that maximising fitness levels in middle-aged men is an important thing to do for a whole raft of reasons. It is likely that slowing atherosclerosis can be added to these. More and better sports facilities should be on somebody's shopping list.

References:
1 TA Lakka et al. Cardiorespiratory fitness and the progression of carotic atherosclerosis in middle-aged men. Annals of Internal Medicine 2001 134: 12-20.



**EDITORS**

Andrew Moore Henry McQuay

Pain Relief Unit
The Churchill, Oxford OX3 7LJ

Editorial office: 01865 226132
Editorial fax: 01865 226978
Email: andrew.moore@pru.ox.ac.uk
Internet: www.ebandolier.com
ISSN 1353-9906